WO0114368

Publication Title:

COMPOUNDS, COMPOSITIONS AND METHODS FOR TREATING INFLUENZA

Abstract:

Pyrazolo[3,4-f]indazole-3,7-dione derivatives are useful in prophylaxis and treatment of influenza virus infection.

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 March 2001 (01.03.2001)

PCT

(10) International Publication Number
WO 01/14368 A1

(51) International Patent Classification[7]: C07D 403/12, 413/12, 417/12, 487/04, A61K 31/416, 31/4162

(21) International Application Number: PCT/US00/23062

(22) International Filing Date: 23 August 2000 (23.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/150,763 26 August 1999 (26.08.1999) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/14368 A1

(54) Title: COMPOUNDS, COMPOSITIONS AND METHODS FOR TREATING INFLUENZA

(57) Abstract: Pyrazolo[3,4-f]indazole-3,7-dione derivatives are useful in prophylaxis and treatment of influenza virus infection.

COMPOUNDS, COMPOSITIONS AND METHODS FOR TREATING INFLUENZA

By Guy D. Diana

FIELD OF THE INVENTION

The present invention relates to compounds, compositions and methods for the treatment and prevention of influenza infection. In particular, the present invention relates to novel pyrazol[3,4-f]indazole-3,7-dione derivatives, pharmaceutical compositions containing such derivatives and their use in treating and preventing influenza infection and other viral diseases.

BACKGROUND OF THE INVENTION

There are three known types of influenza viruses which affect human beings: Influenza A, B and C. Influenza A viruses have been isolated from many animal species in addition to humans, while the influenza B and C viruses infect mainly humans. The influenza viruses are enveloped viruses containing negative single-stranded RNA's which are segmented and encapsidated. The influenza virus envelope is characterized by the presence of two surface glycoproteins: hemagglutinin and neuraminidase. The influenza A and B virions are pleomorphic and are usually 80-120 nm in diameter. The influenza C virion has many distinctive properties and is thus distinguished from the closely related A and B virions. Infection with influenza A or B often can cause a highly contagious, acute respiratory illness.

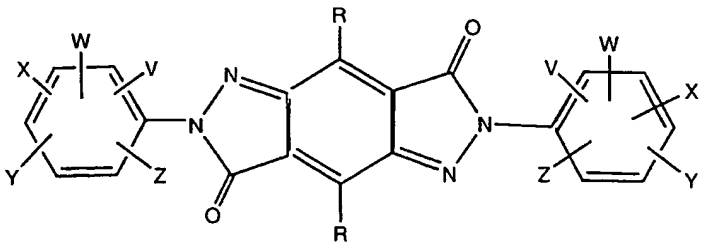
Influenza viruses have a major impact on morbidity leading to increases in hospitalization and visits to health care providers. High rates of hospitalization are observed for patients over 65 years of age and also for children less than 5 years of age. Influenza virus is also unique among respiratory viruses in being a cause of excess mortality. Furthermore, the spread of influenza virus through a population can result in epidemics which have considerable economic impact. For example, high rates of mortality were observed due to influenza infection during the influenza epidemics of 1957, 1968 and 1977. Fields Virology, Second Edition, Volume 1, pp. 1075-1152 (1990).

There are relatively few known compounds that have significant antiviral activity against influenza viruses. Two of these, amantadine and rimantadine, are approved in the United States for the treatment of influenza virus disease. Both compounds are most effective when used prophylactically and influenza viruses develop resistance to both compounds rapidly. See U.S. Patent Nos. 3,152,180 and 3,352,912. Zanamivir, a neuraminidase inhibitor, was recently approved in the United States for treating influenza virus disease. See U.S. Patent No. 5,360,817. Other compounds reported to have activity against influenza viruses are disclosed in U.S. Patents Nos. 3,483,254, 3,496,228, 3,538,160, 3,534,084 and 3,592,934. See also U.S. Patents Nos. 5,684,024 and 5,821,243, which are commonly owned with the present application.

Pyrazolo[3,4-f]indazole-3,7-dione derivatives have been disclosed as having utility as plastic colorants in photography and in the graphic arts. See, for example, U.S. Patent 2,739,153. Insofar as is known, however, such derivatives have not been previously reported as being useful for the treatment or prevention of influenza infection.

SUMMARY OF THE INVENTION

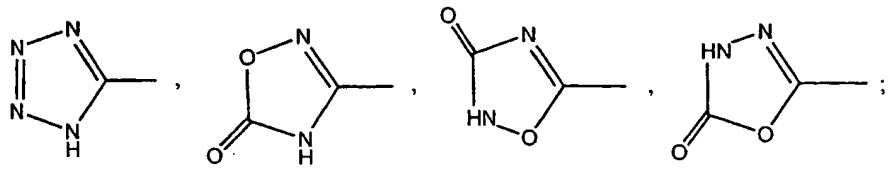
In accordance with one aspect, the present invention provides compounds, including isomeric forms, of the following structure:



(I)

wherein R represents an alkyl (C_1-C_6) radical which may be straight or branched;

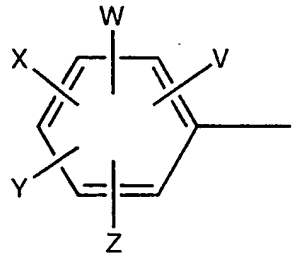
V represents a substituent selected from the group consisting of $COOR_1$, $CONR_2R_3$, $SO_2NR_4R_5$ and



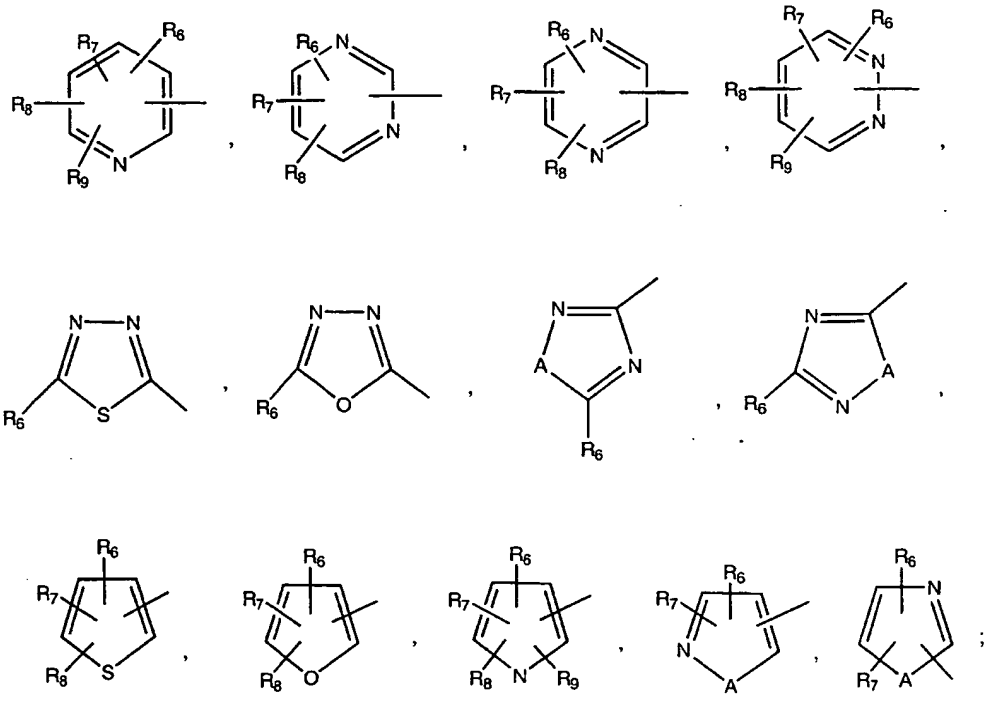
W, X, Y and Z represent the same or different substituents selected from the group consisting of hydrogen, alkyl (C_1-C_6), halogen, monohaloalkyl, dihaloalkyl, perhaloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, COOR′ and CONR″R‴;

R_1 and R′ are the same or different and represent hydrogen or an alkyl (C_1-C_6) radical;

R_2, R_3, R_4, R_5, R″ and R‴ are the same or different and represent hydrogen or an alkyl, aryl, aralkyl, heterocyclic, heterocyclicalkyl, acyl or carboxyalkyl radical, said aryl radical and the aryl moiety of said aralkyl radical having the formula:



wherein V, W, X, Y and Z are as previously defined, said heterocyclic radical or the heterocyclic moiety of said heterocyclicalkyl radical having the formula:



, wherein A is selected from the group consisting of carbon, nitrogen, sulphur or oxygen and R_6, R_7, R_8, and R_9 are the same or different and represent hydrogen, alkyl (C_1-C_6), halogen, monohaloalkyl, dihaloalkyl, perhaloalkyl, thio, alkoxy, alkylthio, alkylamino, dialkylamino, COOH, $CONH_2$ and SO_2 and H_2 and the pharmaceutically acceptable salts of said compound.

According to still another aspect, the present invention provides pharmaceutical compositions comprising one or more of the above-described pyrazolo[3,4 f]indazole-3,7-dione derivatives in combination with a pharmaceutically acceptable carrier medium.

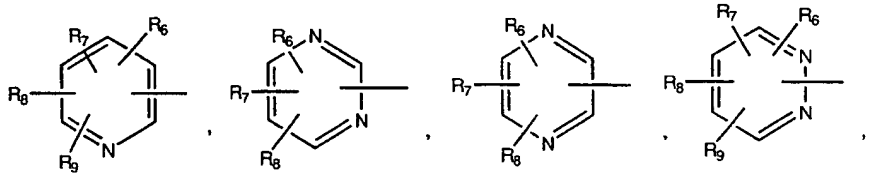
In accordance with yet another aspect, the present invention provides methods for treating and preventing viral influenza infections in living hosts by administering an effective amount of the compounds of the invention to a host susceptible to influenza infection or suffering from such an infection.

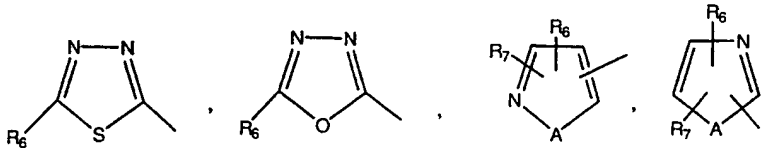
DETAILED DESCRIPTION OF THE INVENTION

The compounds of the invention can be conveniently prepared from known starting materials and specific embodiments of anti-influenza compounds within the scope of the invention are exemplified below.

In vitro studies demonstrating the usefulness of the compounds of the invention as antiviral agents against the influenza virus have been performed. Antiviral activity was measured on the basis of inhibition of influenza virus transcriptase. The method for determining the antiviral activity of the compounds of the invention is described in the examples that follow.

Among the particularly preferred embodiments of the invention are compounds, including isomeric forms, having formula I, above, wherein R represents methyl, V represents $-SO_2NHR_4$,W, X, Y and Z are selected from the group consisting of hydrogen, alkyl, alkoxy, trifluoromethyl and difluoromethyl and R_4 represents a heterocylic group having the formula:





, wherein A is as previously defined and R_6, R_7, R_8 and R_9 are the same or different and represent hydrogen, alkyl, alkoxy, trifluoromethyl or difluoromethyl, and the pharmaceutically acceptable salts of such compound.

The compounds of the present invention do not include those of formula I, above, in which V represents para-$SO_2NR_4R_5$, and R_4 and R_5 both represent hydrogen, or in which V represents COOH and one of W, X, Y or Z also represents COOH. Such compounds are the subject of expired U.S. Patent

2,739,153. However, the use of such compounds for the treatment or prevention of influenza virus infection is within the scope of this invention.

The term "alkyl" as used herein refers to straight or branched aliphatic hydrocarbon radicals of one to six carbon atoms in length. Similarly, the term "alkyl", or any variation thereof, used in combination form to name substituents, such as alkoxy (-O-alkyl), alkylthio (-S-alkyl), alkylamino (-NH-alkyl), alkylsulfonyl (-$S(O)_2$-alkyl), carboxyalkyl (-alkyl-COOH), or the like, also refers to aliphatic hydrocarbon radicals of one to six carbon atoms in length, and preferably of one to four carbon atoms in length.

The term "acyl" is used herein in accordance with its ordinary meaning to refer to an organic radical derived from a carboxylic acid by the removal of the hydroxyl group, such as acetyl, benzoyl or the like.

Isomers of the compound of formula I, above, that are within the scope of the invention include, without limitation, tautomeric forms of such compound.

As previously noted, the compounds of formula I, above, including their pharmaceutically acceptable salts, exhibit antiviral activity against influenza virus and are useful in treating and/or preventing infections or diseases associated with these viruses in living hosts.

The compounds of the invention or precursors (e.g., prodrugs) thereof and their pharmaceutically acceptable salts are also useful in treating and preventing viral infections and diseases in living hosts when used in combination with other active agents, including but not limited to interferons, ribavirin, amantadine, rimantadine, neuraminidase inhibitors, protease inhibitors, immunoglobulins, immunomodulators, anti-inflammatory agents, antibiotics, antivirals, anti-infectious agents, and the like.

Compounds described herein are also useful in preventing or resolving viral infections in cell, tissue or organ cultures and other *in vitro* applications. For example, inclusion of compounds of the invention as a supplement in cell or tissue culture growth media and cell or tissue culture components will prevent viral infections or contaminations of cultures not previously infected with viruses. Compounds described above may also be used

to eliminate viruses from cultures or other biological materials infected or contaminated with viruses (e.g., blood), after a suitable treatment period, under any number of treatment conditions as determined by the skilled artisan.

The compounds of the invention can form salts with inorganic and organic bases, including, for example, alkali metal salts, such as Na or K salts, alkaline earth metal salts, such as Ca or Mg salts, ammonium, substituted ammonium and other amine salts such as morpholine, piperidine or pyridine salts. Acid salts of the compounds described above also have antiviral activity. Suitable salt forming acids include both inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, methyl sulfonic acid or the like.

The pharmaceutically acceptable salts of the compounds of Formula I are prepared following procedures which are familiar to those skilled in the art.

The antiviral pharmaceutical compositions of the present invention comprise one or more of the compounds of formula I above, as the active ingredient in combination with a pharmaceutically acceptable carrier medium or auxiliary agent.

The composition may be prepared in various forms for administration, including tablets, caplets, pills or dragees, or can be filled in suitable containers, such as capsules, or, in the case of suspensions, filled into bottles. As used herein, "pharmaceutically acceptable carrier medium" includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Fifteenth Edition, E.W. Martin (Mack Publishing Co., Easton, PA, 1975) discloses various carriers used in formulating pharmaceutical compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the anti-viral compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition, its use is contemplated to be within the scope of this invention.

In the pharmaceutical compositions of the invention, the active agent may be present in an amount of at least 0.5% and not more than 90% by weight based on the total weight of the composition, including carrier medium and/or auxiliary agent(s). Preferably, the proportion of active agent various between 5 to 50% by weight of the composition.

Pharmaceutical organic or inorganic solid or liquid carrier media suitable for enteral or parenteral administration can be used to make up the composition. Gelatine, lactose, starch, magnesium stearate, talc, vegetable and animal fats and oils, gum, polyalkylene glycol, or other known medicament components may all be suitable as carrier media or excipients.

The compounds of the invention may be administered using any amount and any route of administration effective for attenuating infectivity of the influenza virus. Thus, the expression "amount effective to attenuate infectivity of influenza virus", as used herein, refers to a nontoxic but sufficient amount of the antiviral agent to provide the desired treatment of viral infection. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular antiviral agent, its mode of administration, and the like. The anti-influenza compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of antiviral agent appropriate for the patient to be treated. Each dosage should contain the quantity of active material calculated to produce the desired therapeutic effect either as such, or in association with the selected pharmaceutical carrier medium and/or the supplemental active agent(s), if any. Typically, the antiviral compounds of the invention will be administered in dosage units containing from about 0.1 mg to about 500 mg of the antiviral agent, with a range of about 1 mg to about 100 mg being preferred.

The compounds of the invention may be administered as such, or in the form of a precursor from which the active agent can be derived, such as a prodrug. A prodrug is a derivative of a compound described herein, the pharmacologic action of which results from the conversion by chemical or

metabolic processes *in vivo* to the active compound. Prodrugs include, without limitation, esters of the compounds of Formula I, above, having a carboxyl functionality. Such esters may be prepared from simple or functionalized aliphatic alcohols. Such prodrugs may be prepared according to procedures well known in the field of medicinal chemistry and pharmaceutical formulation science.

The compounds may be administered orally, rectally, parenterally, such as by intramuscular injection, subcutaneous injection, intravenous infusion or the like, intracisternally, intravaginally, intraperitoneally, locally, such as by powders, ointments, drops or the like, or by inhalation, such as by aerosol or the like, depending on the nature and severity of the infection being treated. Depending on the route of administration, the compounds of the invention may be administered at dosage levels of about 10^{-3} to about 120 mg/kg of subject body weight per day and preferably from about 10^{-2} to about 30 mg/kg of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect. By way of example, a suitable dose for oral administration would be on the order of 30 mg/kg of body weight per day, whereas a typical dose for inhalation would be on the order of 10^{-2} mg/kg of body weight per day.

Although the pyrazolo[3,4-f]indazole-3,7-dione derivatives described herein can be administered to any host which is susceptible to influenza infection, the compounds are intended for the treatment of mammalian hosts, and especially humans.

The compounds of the invention will typically be administered from 1 to 4 times a day so as to deliver the above-mentioned daily dosage. However, the exact regimen for administration of the compounds and compositions described herein will necessarily be dependent on the needs of the individual host being treated, the type of treatment administered and the judgment of the attending medical specialist.

In view of the inhibitory effect on influenza virus transcriptase produced by the compounds of the invention, it is anticipated that these compounds will be useful not only for therapeutic treatment of infection, but for influenza viral prophylaxis, as well. The above-noted dosages will be essentially

the same whether for treatment or prophylaxis of influenza infection.

The following examples are provided to describe the invention in further detail. These examples, which set forth the best mode presently contemplated for carrying out the invention, are intended to illustrate and not to limit the invention.

Example 1 illustrates the chemical synthesis of a compound which is considered to be a representative embodiment of the invention. Any reference to acidification in the example indicates that the intermediate or the compound of the invention was acidified to pH 3.0. The expression "concentrated hydrochloric acid", as used in the example, refers to 3N HCl.

EXAMPLE 1

(4,8-Dimethyl-2,3,6,7-tetrahydro-3,7-dioxo-pyrazolo [3,4 *f*]indazol-2,6-diyl)bis(4-phenylcarbonylaminopropionic acid)

a.) **4-(3-Acetyl-4,5-dihydro-5-oxo-pyrazol-1-yl)phenylcarbonylaminopropionic acid** - To a solution of 4.16 g (20 mmol) of commercially available 3-(4-amino-benzoylamino)propionic acid in 50 ml of ethanol and 50 ml of H_2O containing 4.4 ml of conc. HCl at 5°C was added dropwise a solution of 2.8 g (22 mmol) of sodium nitrite in 30 ml of H_2O. After warming to room temperature, a solution of 4.1 g (22 mmol) of ethyl 3-acetyl-4-oxypentanoate and 8.1 ml of pyridine was added. The red solution was allowed to stir at room temperature for 4 hours, diluted with water (300 ml), and acidified with 1N HCl (100 ml). The precipitate was collected by filtration, washed with water, and rinsed with hexanes to afford 4.0 g of the hydrazone intermediate. A suspension of this 4.0 g of the hydrazone intermediate in 25 ml of 1 N NaOH was sonicated for 10 minutes producing a red solution. Upon acidification with 1 N HCl, a gray precipitate formed. Filtration provided 3.2 g of the product as a dark gray solid, mp >250°C.

b.) **(4,8-Dimethyl-2,3,6,7-tetrahydro-3,7-dioxo-pyrazolo[3,4-f] indazol-2,6-diyl)bis(4-phenylcarbonylaminopropionic acid)** - A mixture containing 0.1 g (0.3 mmol) of 4-(3-Acetyl-4,5-dihydro-5-oxo-pyrazol-1-

yl)phenylcarbonylaminopropionic acid, 0.5 g (0.8 mmol) of acetamide, and 0.25 ml of acetic acid was heated at 110°C for 1 hour. Upon cooling to room temperature, the purple reaction mixture was diluted with water (10 ml) and filtered. The solid was washed successively with water and hexanes to afford 98.2 mg of the product.

Other aromatic amine derivatives may be reacted with a β, β-diacetyl propionate ester to yield a variety of substituted 3-acyl pyrazolones. These undergo bimolecular condensation, under the conditions described in Example 1, above, resulting in additional pyrazolo[3,4 f]indazole-3,7-dione derivatives within the scope of this invention. Representative examples of such compounds are set forth in the table below.

EXAMPLE NO.	COMPOUND NAME
2	(4,8-Dimethyl-2,3,6,7-tetrahydro-3,7-dioxo-pyrazolo[3,4-f]indazol-2,6-diyl)bis (4-(N-pyrimidinyl)benzenesulfonamide)
3	(4,8-Dimethyl-2,3,6,7-tetrahydro-3,7-dioxo-pyrazolo[3,4-f]indazol-2,6-diyl)bis (3-tetrazolylbenzene)
4	(4,8-Dimethyl-2,3,6,7-tetrahydro-3,7-dioxo-pyrazolo[3,4-f]indazol-2,6-diyl)bis (4-(N-1,3,4-thiadiazolyl)benzenesulfonamide)
5	(4,8-Dimethyl-2,3,6,7-tetrahydro-3,7-dioxo-pyrazolo[3,4-f]indazol-2,6-diyl)bis (4-(N-isoxazolyl)benzenesulfonamide)
6	(4,8-Dimethyl-2,3,6,7-tetrahydro-3,7-dioxo-pyrazolo[3,4-f]indazol-2,6-diyl)bis (4-tetrazolylbenzene)
7	(4,8-Dimethyl-2,3,6,7-tetrahydro-3,7-dioxo-pyrazolo[3,4-f]indazol-2,6-diyl)bis (3-(-p-methoxy)benzoic acid)

8	(4,8-Dimethyl-2,3,6,7-tetrahydro-3,7-dioxo-pyrazolo[3,4-f]indazol-2,6-diyl)bis (3(-p-methyl)benzamide)
9	(4,8-Dimethyl-2,3,6,7-tetrahydro-3,7-dioxo-pyrazolo[3,4-f]indazol-2,6-diyl)bis (3-benzenesulfonamide)

EXAMPLE 1I

INHIBITION OF VIRAL REPLICATION

An assay for influenza A/WSN virus transcription was performed with detergent-treated purified influenza virions and rabbit globin messenger RNA according to the following procedure. Duplicate reactions (50 μl in 96 well polypropylene U-bottom plates) contained 50 mM Hepes, pH 8, 5 mM dithiothreitol (DTT), 5 mM magnesium chloride, 0.02% Triton X-100, 30 μM ATP, 0.3 μM CTP, 0.5 μM GTP, 2 μCi 35S-UTP (Amersham SJ1303), 0.75 μg (15 μg/ml) purified virions, and 50 ng of rabbit globin messenger RNA. Test compounds were solubilized with 100% dimethylsulfoxide (DMSO) and were present in the reactions at 1% DMSO. Incubation was for 45 minutes at 31°C. Reactions were stopped by the addition of 150 μl of ice-cold 7% trichloracetic acid (TCA) + 2% sodium pyrophosphate containing 50 μg/ml yeast tRNA. The TCA precipitates were filtered onto Millipore HATF plates pre-wetted with 200 μl of 7% TCA + 2% sodium pyrophosphate without yeast tRNA. Plates were washed four times with 5% TCA + 2% sodium pyrophosphate and filters were dried and punched onto pressure sensitive film, and quantitated using a Molecular Dynamics Storm System.

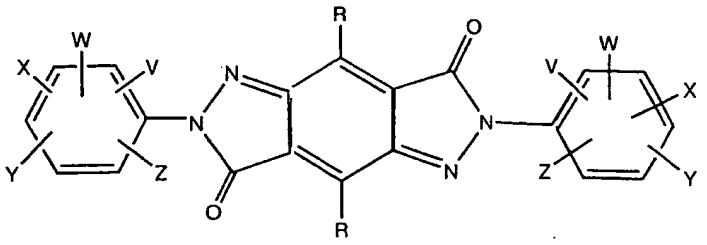
Representative compounds within the scope of the present invention, as shown in Example 1 and the foregoing table, were evaluated for antiviral activity in assay described above. A measure of the inhibitory activity of compounds of the invention may be expressed as IC_{50} values. IC_{50} values represent the concentration of the compound required to achieve a 50% inhibition of influenza A/WSN virus transcriptase activity. The results of the assay for

inhibition of viral transcriptase activity of the compounds tested revealed IC_{50} values ranging from 0.3 to about 25 μM. These low concentrations of test compounds required to achieve 50% inhibition of viral transcriptase activity indicate that the compounds of the invention are effective at inhibiting the influenza A/WSN virus transcription process.

Although the present invention has been described and exemplified in terms of certain preferred embodiments, other embodiments will be apparent to those skilled in the art. The invention is, therefore, not limited to the particular embodiments described and exemplified, but is capable of modification or variation without departing from the spirit of the invention, the full scope of which is delineated by the appended claims.

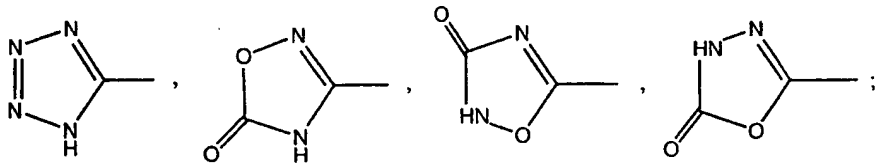
WHAT IS CLAIMED IS:

1. A compound having the formula:



wherein R represents an alkyl (C_1-C_6) radical which may be straight or branched;

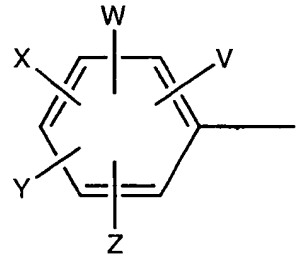
V represents a substituent selected from the group consisting of $COOR_1$, $CONR_2R_3$, $SO_2NR_4R_5$ and



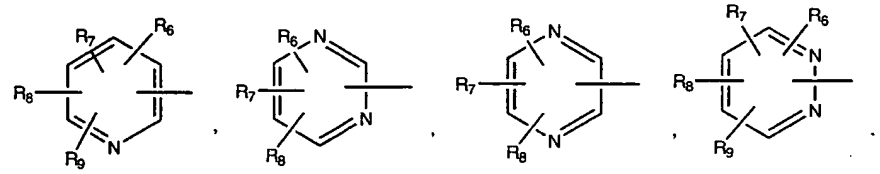
W, X, Y and Z represent the same or different substituents selected from the group consisting of hydrogen, alkyl (C_1-C_6), halogen, monohaloalkyl, dihaloalkyl, perhaloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, COOR′ and CONR″R‴;

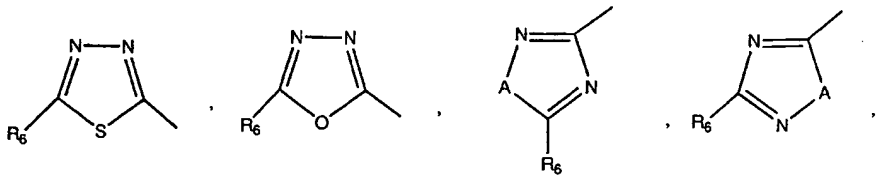
R_1 and R′ are the same or different and represent hydrogen or an alkyl (C_1-C_6) radical;

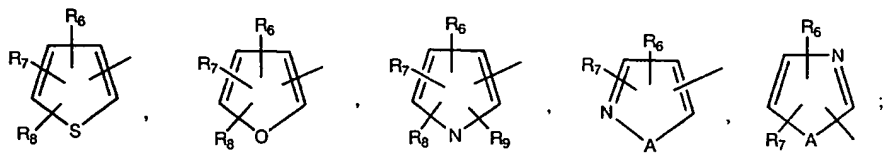
R_2, R_3, R_4, R_5, R″ and R‴ are the same or different and represent hydrogen or an alkyl, aryl, aralkyl, heterocyclic, heterocyclicalkyl, acyl or carboxyalkyl radical, said aryl radical and the aryl moiety of said aralkyl radical having the formula:



wherein V, W, X, Y and Z are as previously defined, said heterocyclic radical or the heterocyclic moiety of said heterocyclicalkyl radical having the formula:

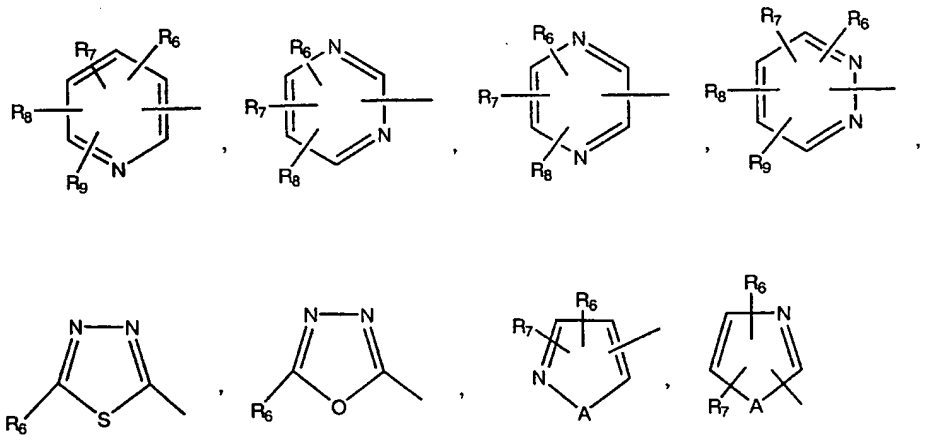






, wherein A is selected from the group consisting of carbon, nitrogen, sulphur or oxygen and R_6, R_7, R_8, and R_9 are the same or different and represent hydrogen, alkyl (C_1-C_6), halogen, monohaloalkyl, dihaloalkyl, perhaloalkyl, thio, alkoxy, alkylthio, alkylamino, dialkylamino, COOH, $CONH_2$ and SO_2NH_2; and with the proviso that when V in the above formula represents para-$SO_2NR_4R_5$, R_4 and R_5 do not both represent hydrogen and that when V in the above formula represents COOH, none of W, X, Y or Z represents COOH; and the isomers and pharmaceutically acceptable salts of said compound.

2. A compound as claimed in claim 1, wherein R represents methyl, V represents -SO_2NHR_4, W, X, Y and Z are selected from the group consisting of hydrogen, alkyl, alkoxy, trifluoromethyl and difluoromethyl and R_4 represents a heterocylic group having the formula:



, wherein R_6, R_7, R_8 and R_9 are the same or different and represent hydrogen, alkyl, alkoxy, trifluoromethyl or difluoromethyl.

3. The compound (4,8-dimethyl-2,3,6,7-tetrahydro-3,7-dioxo-pyrazolo[3,4-f]indazol-2,6-diyl)bis (4-(N-pyrimidinyl)benzenesulfonamide), as claimed in claim 1.

4. The compound (4,8-dimethyl-2,3,6,7-tetrahydro-3,7-dioxo-pyrazolo[3,4-f]indazol-2,6-diyl)bis (3-tetrazolylbenzene), as claimed in claim 1.

5. The compound (4,8-dimethyl-2,3,6,7-tetrahydro-3,7-dioxo-pyrazolo[3,4-f]indazol-2,6-diyl)bis (4-(N-1,3,4-thiadiazolyl)benzenesulfonamide), as claimed in claim 1.

6. The compound (4,8-dimethyl-2,3,6,7-tetrahydro-3,7-dioxo-pyrazolo[3,4-f]indazol-2,6-diyl)bis (4-(N-isoxazolyl)benzenesulfonamide), as claimed in claim 1.

7. The compound (4,8-dimethyl-2,3,6,7-tetrahydro-3,7-dioxo-pyrazolo[3,4-f]indazol-2,6-diyl)bis (4-phenylcarbonylamino propionic acid), as claimed in claim 1.

8. The compound (4,8-dimethyl-2,3,6,7-tetrahydro-3,7-dioxo-pyrazolo[3,4-f]indazol-2,6-diyl)bis (4-tetrazolylbenzene), as claimed in claim 1.

9. The compound (4,8-dimethyl-2,3,6,7-tetrahydro-3,7-dioxo-pyrazolo[3,4-f]indazol-2,6-diyl)bis (3-(p-methoxy)benzoic acid), as claimed in claim 1.

10. The compound (4,8-dimethyl-2,3,6,7-tetrahydro-3,7-dioxo-pyrazolo[3,4-f]indazol-2,6-diyl)bis (3-(-p-methyl)benzamide), as claimed in claim 1.

11. The compound (4,8-dimethyl-2,3,6,7-tetrahydro-3,7-dioxo-pyrazolo[3,4-f]indazol-2,6-diyl)bis (3-benzenesulfonamide), as claimed in claim 1.

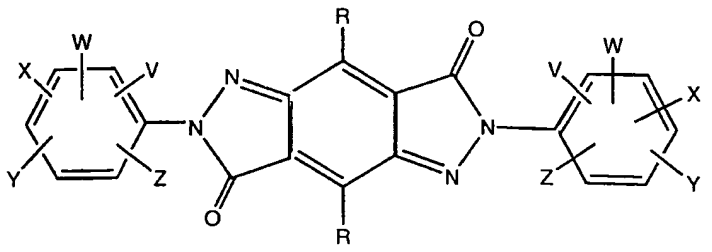
12. A pharmaceutical composition for treating or preventing influenza virus infection, said composition comprising a compound as claimed in claim 1 in an amount effective to attenuate infectivity of said virus, and a pharmaceutically acceptable carrier medium.

13. A composition as claimed in claim 12 in the form of a solid with a pharmaceutically acceptable excipient.

14. A composition as claimed in claim 12 in the form of a liquid with a pharmaceutically acceptable diluent.

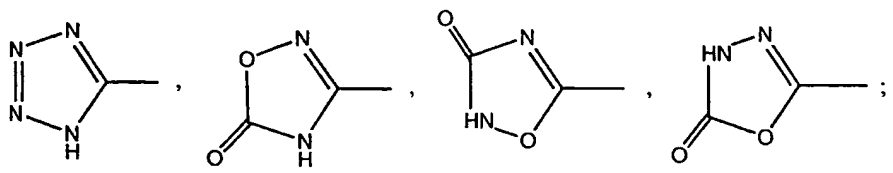
15. A composition as claimed in claim 12 in dosage unit form comprising per unit from about 0.1 mg to about 500 mg of said compound.

16. A method of treating influenza virus infection in a living host in need of said treatment, said method comprising administering to said living host a therapeutically effective amount of a compound having the formula:



, or a precursor of said compound, wherein R represents an alkyl (C_1-C_6) radical which may be straight or branched;

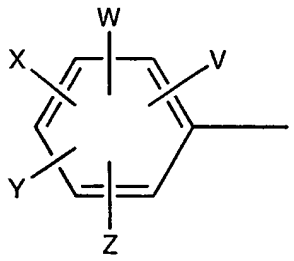
V represents a substituent selected from the group consisting of $COOR_1$, $CONR_2R_3$, $SO_2NR_4R_5$ and



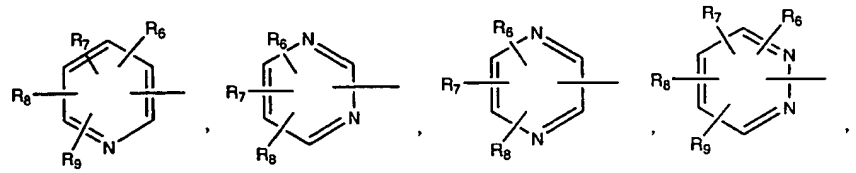
W, X, Y and Z represent the same or different substituents selected from the group consisting of hydrogen, alkyl (C_1-C_6), halogen, monohaloalkyl, haloalkyl, perhaloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, COOR' and CONR"R'";

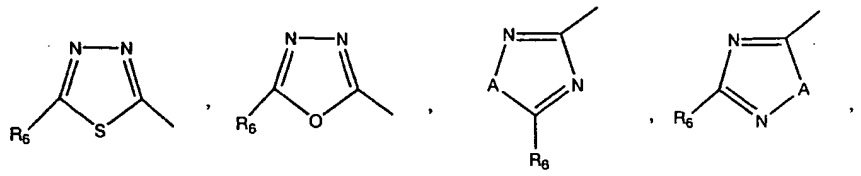
R_1 and R' are the same or different and represent hydrogen or an alkyl (C_1-C_6) radical;

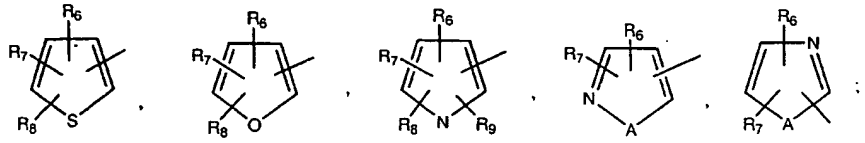
R_2, R_3, R_4, R_5, R" and R'" are the same or different and represent hydrogen or an alkyl, aryl, aralkyl, heterocyclic, heterocyclicalkyl, acyl or carboxyalkyl radical, said aryl radical and the aryl moiety of said aralkyl radical having the formula:



wherein V, W, X, Y and Z are as previously defined, said heterocyclic radical or the heterocyclic moiety of said heterocyclicalkyl radical having the formula:







, wherein A is selected from the group consisting of carbon, nitrogen, sulphur or oxygen and R_6, R_7, R_8, and R_9 are the same or different and represent hydrogen, alkyl (C_1-C_6), halogen, monohaloalkyl, dihaloalkyl, perhaloalkyl, thio, alkoxy, alkylthio, alkylamino, dialkylamino, COOH, $CONH_2$ and SO_2NH_2; and the isomers and pharmaceutically acceptable salts of said compound.

17. A method as claimed in claim 16, wherein said compound is administered in unit dosage form containing about 10^{-3} mg to about 120 mg of said compound per kilogram of host body weight per day.

18. A method as claimed in claim 17, wherein said unit dosage includes a pharmaceutically carrier medium.

19. A method as claimed in claim 16, wherein a precursor of said compound is administered in the form of a prodrug.

20. A method as claimed in claim 16, wherein said compound or precursor of said compound is administered together, either simultaneously or sequentially, with at least one other therapeutic agent.

21. A method as claimed in claim 20, wherein said other therapeutic agent is selected from the group consisting of interferons, ribavirin, amantadine, rimantadine, neuraminidase inhibitors, protease inhibitors, immunoglobulins, immunomodulators, anti-inflammatory agents, antibiotics, antivirals and anti-infectious agents.

22. A method as claimed in claim 16, wherein said compound or a precursor of said compound is administered orally.

23. A method as claimed in claim 16, wherein said compound or a precursor of said compound is administered rectally.

24. A method as claimed in claim 16, wherein said compound is administered parenterally.

25. A method as claimed in claim 16, wherein said compound is administered intracisternally.

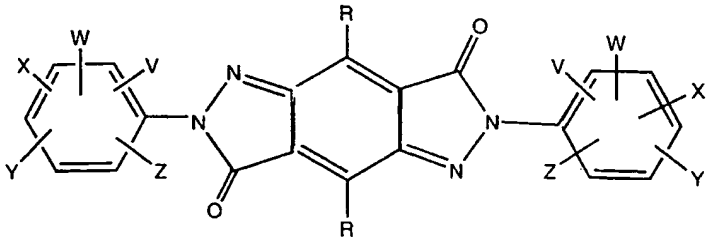
26. A method as claimed in claim 16, wherein said compound is administered intravaginally.

27. A method as claimed in claim 16, wherein said compound is administered intraperitoneally.

28. A method as claimed in claim 16, wherein said compound is administered locally.

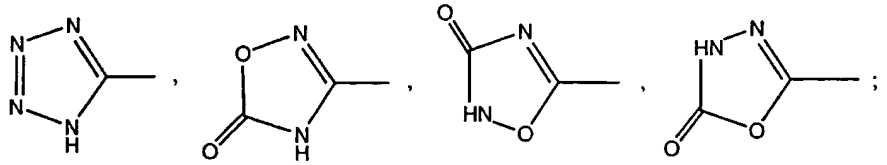
29. A method as claimed in claim 16, wherein said compound is administered by inhalation.

30. A method of preventing influenza virus infection in a living host susceptible to said infection, said method comprising administering to said host a prophylactically effective amount of a compound having the formula:



, or a precursor of said compound, wherein R represents an alkyl (C_1-C_6) radical which may be straight or branched;

V represents a substituent selected from the group consisting of $COOR_1$, $CONR_2R_3$, $SO_2NR_4R_5$ and

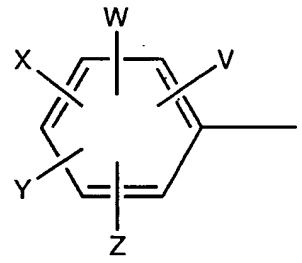


W, X, Y and Z represent the same or different substituents selected from the group consisting of hydrogen, alkyl (C_1-C_6), halogen, monohaloalkyl, dihaloalkyl, perhaloalkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, COOR' and CONR"R'";

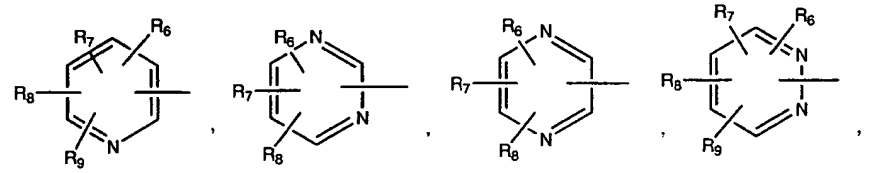
R_1 and R' are the same or different and represent hydrogen or an alkyl (C_1-C_6) radical;

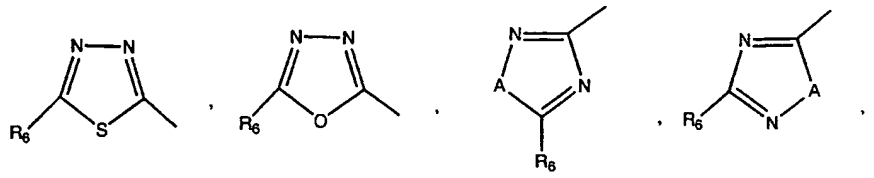
R_2, R_3, R_4, R_5, R" and R'" are the same or different and represent hydrogen or an alkyl, aryl, aralkyl, heterocyclic, heterocyclicalkyl, acyl or

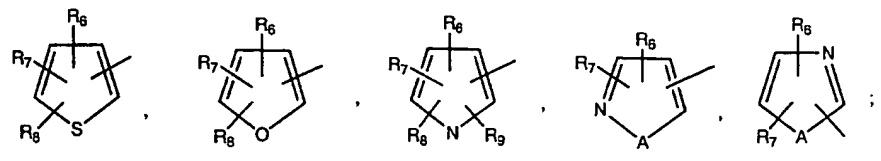
carboxyalkyl radical, said aryl radical and the aryl moiety of said aralkyl radical having the formula:



wherein V, W, X, Y and Z are as previously defined, said heterocyclic radical or the heterocyclic moiety of said heterocyclicalkyl radical having the formula:







, wherein A is selected from the group consisting of carbon, nitrogen, sulphur or oxygen and R_6, R_7, R_8, and R_9 are the same or different and represent hydrogen, alkyl (C_1-C_6), halogen, monohaloalkyl, dihaloalkyl, perhaloalkyl, thio, alkoxy, alkylthio, alkylamino, dialkylamino, COOH, $CONH_2$ and SO_2NH_2 and the isomers and pharmaceutically acceptable salts of said compound.

31. A method as claimed in claim 30, wherein said compound is administered in unit dosage form containing about 10^{-3} mg to about 120 mg of said compound per kilogram of patient body weight per day.

32. A method as claimed in claim 31, wherein said unit dosage includes a pharmaceutically acceptable carrier medium.

33. A method as claimed in claim 30, wherein a precursor of said compound is administered in the form of a prodrug.

34. A method as claimed in claim 30, wherein said compound or precursor of said compound is administered together, either simultaneously or sequentially, with at least one therapeutic agent.

35. A method as claimed in claim 34, wherein said other therapeutic agent is selected from the group consisting of interferons, ribavirin, protease inhibitors, immunoglobulins, immunomodulators, amantadine, rimantadine, neuraminidase inhibitors, anti-inflammatory agents, antibiotics, antivirals and anti-infectious agents.

36. A method as claimed in claim 30, wherein said compound or a precursor of said compound is administered orally.

37. A method as claimed in claim 30, wherein said compound or a precursor of said compound is administered rectally.

38. A method as claimed in claim 30, wherein said compound or a precursor of said compound is administered parenterally.

39. A method as claimed in claim 30, wherein said compound or a precursor of said compound is administered intracisternally.

40. A method as claimed in claim 30, wherein said compound or a precursor of said compound is administered intravaginally.

41. A method as claimed in claim 30, wherein said compound or a precursor of said compound is administered intraperitoneally.

42. A method as claimed in claim 30, wherein said compound or a precursor of said compound is administered locally.

43. A method as claimed in claim 30, wherein said compound or a precursor of said compound is administered by inhalation.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/23062

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C07D 403/12, 413/12, 417/12, 487/04; A61K 31/416, 31/4162
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/275, 363, 364, 380, 381, 405; 544/327, 331; 548/132, 138, 144, 245, 250, 252, 359.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chem. abstr., Vol. 116, No. 8, 24 February 1992 (Columbus, OH, USA), page 108, column 1, the abstract No. 61551r, NAEF, R. 'Synthesis, porton-NMR and electronic absorption spectra of 2,6-disubstituted derivatives of 2,6-dihydrobenz[1,2-c:4,5-c']dipyrazol-3,7-dione, a new cross-conjugated chromophore.' Dyes Pigm., 1991, 17(2), 113-21 (Eng).	1
A	US 5,684,024 A (DIANA ET AL) 04 November 1997 (04/11/97), see entire document.	1-43
A	US 5,821,243 A (DIANA ET AL) 13 October 1998 (13/10/98), see entire document.	1-43

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 OCTOBER 2000	14 NOV 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT	Authorized officer Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/23062

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/275, 363, 364, 380, 381, 405; 544/327, 331; 548/132, 138, 144, 245, 250, 252, 359.5